

General

Guideline Title

Diagnosis and treatment of headache.

Bibliographic Source(s)

Beithon J, Gallenberg M, Johnson K, Kildahl P, Krenik J, Liebow M, Linbo L, Myers C, Peterson S, Schmidt J, Swanson J. Diagnosis and treatment of headache. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jan. 90 p. [140 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of headache. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Jan. 84 p.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines](#) : A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- [March 22, 2016 – Opioid pain medicines](#) : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has

changed since the previous version of this guidance, refer to Summary of Changes Report -- January 2013 (see the "Guideline Availability" field). In addition, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. This document is in transition to the GRADE methodology. Transition steps incorporating GRADE methodology for this document include the following:

- Priority placed upon available systematic reviews in literature searches.
- All existing Class A (randomized controlled trials [RCTs]) studies have been considered as high quality evidence unless specified differently by a work group member.
- All existing Class B, C and D studies have been considered as low quality evidence unless specified differently by a work group member.
- All existing Class M and R studies are identified by study design versus assigning a quality of evidence. Refer to Crosswalk between ICSI Evidence Grading System and GRADE (see below in the "Definitions" section).
- All new literature considered by the work group for this revision has been assessed using GRADE methodology.

The recommendations for the diagnosis and treatment of headache are presented in the original guideline document in the form of 10 algorithms with 131 components, accompanied by detailed annotations (see the "Guideline Availability" field). In addition to a Main algorithm, algorithms are provided for: Diagnosis; Migraine Treatment; Tension-Type Headache; Cluster Headache; Dihydroergotamine Mesylate; Menstrual-Associated Migraine; Perimenopausal or Menopausal Migraine; On Estrogen-Containing Contraceptives or Considering Estrogen-Containing Contraceptives with Migraine; Migraine Prophylactic Treatment. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Quality of evidence (Low Quality, Moderate Quality, High Quality, Meta-analysis, Systematic Review, Decision Analysis, Cost-Effectiveness Analysis, Guideline, and Reference) and conclusion grade (I-III, Not Assignable) definitions are repeated at the end of the "Major Recommendations" field.

Clinical Highlights

- Headache is diagnosed by history and physical examination with limited need for imaging or laboratory tests. (*Annotation #11; Aim #1*)
- Warning signs of possible disorder other than primary headache are (*Annotation #12; Aim #1*):
 - Subacute and/or progressive headaches which worsen over time (months)
 - A new or different headache
 - Any headache of maximum severity at onset
 - Headache of new onset after age 50
 - Persistent headache precipitated by a Valsalva maneuver
 - Evidence such as fever, hypertension, myalgias, weight loss, or scalp tenderness suggesting a systemic disorder
 - Presence of neurological signs that may suggest a secondary cause
 - Seizures
- Migraine-associated symptoms are often misdiagnosed as "sinus headache" by patients and clinicians. Most headaches characterized as "sinus headaches" are migraines. (*Annotation #15; Aim #1*)
- Early treatment of migraines with effective medications improves a variety of outcomes including duration, severity and associated disability. (*Annotations #32, 36; Aim #7*)
- Drug treatment of acute headache should generally not exceed more than two days per week on a regular basis. More frequent treatment other than this may result in medication-overuse chronic daily headaches. (*Annotation #32, 36; Aim #7*)
- Inability to work or carry out usual activities during a headache is an important issue for migraineurs. (*Annotation #30; Aim #4*)
- Prophylactic therapy should be considered for all patients. (*Annotations #66, 77, 91, 94, 122, 131; Aim #3*)
- Migraines occurring in association with menses and not responsive to standard cyclic prophylaxis may respond to hormonal prophylaxis with use of estradiol patches, creams, or estrogen-containing contraceptives. (*Annotation #94; Aim #3*)
- Women who have migraines with aura have a substantially higher risk of stroke with the use of estrogen-containing contraceptive compared to those without migraines. Headaches occurring during perimenopause or after menopause may respond to hormonal therapy. (*Annotation #109, 111; Aim #5*)
- Most prophylactic medications should be started in a low dose and titrated to a therapeutic dose to minimize side effects and maintained at target dose for 8–12 weeks to obtain maximum efficacy. (*Annotation #122; Aims #3, 5, 7*)

Special Circumstances

Adolescents

At this time the majority of the adolescent literature supports a strong placebo effect in this age group. Success of triptans and prophylactic medications in patients age 12-17 yield similar positive outcomes as in adult studies, but placebo administered in blinded, controlled studies has a

similar effect. There has been a recent study that supports the use of almotriptan with statistically significant efficacy over placebo. As an acute treatment, almotriptan in the dose of 12.5 mg was effective in relieving pain and associated symptoms and was well tolerated [*High Quality Evidence*].

As a prophylactic treatment, topiramate 100 mg/day was effective in reduction of the number of migraine headaches a month [*High Quality Evidence*].

Psychological treatments, principally relaxation and cognitive behavioral therapies are effective treatments of childhood headache [*Meta-analysis/Systematic Review*].

Pregnancy and Breastfeeding

Special consideration should be given to medication selection and management during pregnancy and breastfeeding, considering the risks and benefits of selected drugs and their efficacy.

Diagnosis Algorithm Annotations

10. Patient Presents with Complaint of a Headache

Recommendation

- Clinicians should perform an appropriate prompt evaluation of the patient who presents with headache and initiate acute treatment. Migraine is the most common headache disorder seen by primary care providers [*Low Quality Evidence*].

A patient may present for care of headaches during an attack or during a headache-free period. If a patient presents during a headache, appropriate evaluation (history, examination, appropriate testing) needs to be undertaken in a timely fashion. Once the diagnosis of primary headache is established, acute treatment is instituted. If the patient has a history of recurrent headaches, a plan for treatment (acute and prophylactic) needs to be established.

11. Critical First Steps

Recommendation:

- Clinicians should gather a detailed history, including a focused physical and neurological exam, of the patient who presents with headache.

Minimal general physical examination is performed at the first consultation of patient presenting with a headache. Symptoms and signs with the use of criteria can diagnose headache. The International Classification of Headache Disorders, second edition (ICHD-II) system presently provides the gold standard. As empirical evidence and clinical experience accumulate, criteria for diagnosing headaches will be revised [*Reference*].

Detailed History

Inquire about functional disabilities at work, school, housework, or leisure activities during the past 3 months (informally or using well-validated disability questionnaire).

Assessment of the headache characteristics requires determination of the following:

Temporal profile:

- Time from onset to peak
- Usual time of onset (season, month, menstrual cycle, week, hour of day)
- Frequency and duration
- Stable or changing over past 6 months and lifetime

Autonomic features:

- Nasal stuffiness
- Rhinorrhea
- Tearing
- Eyelid ptosis or edema

Descriptive characteristics: pulsatile, throbbing, pressing, sharp, etc.

Location: uni- or bilateral, changing sides

Severity

Precipitating features and factors that aggravate and/or relieve the headache

Factors that relieve the headache

History of other medical problems

Pharmacological and non-pharmacological treatments which are effective or ineffective

Aura (present in approximately 15% of migraine patients)

Focused Physical Examination

Vital signs (blood pressure, pulse, respirations, and temperature)

Extracranial structure evaluation such as carotid arteries, sinuses, scalp arteries, cervical paraspinal muscles

Examination of the neck in flexion versus lateral rotation for meningeal irritation. (Even a subtle limitation of neck flexion may be considered an abnormality.)

Focused Neurological Examination

A focused neurological examination may be capable of detecting most of the abnormal signs likely to occur in patients with headache due to acquired disease or a secondary headache.

This exam should include at least the following evaluations:

- Assessment of patient's awareness and consciousness, presence of confusion, and memory impairment
- Ophthalmological examination to include pupillary symmetry and reactivity, optic fundi, visual fields, and ocular motility
- Cranial nerve examination to include corneal reflexes, facial sensation, and facial symmetry
- Symmetry of muscle tone, strength (may be as subtle as arm or leg drift), or deep tendon reflexes
- Sensation
- Plantar response(s)
- Gait, arm and leg coordination

12. Causes for Concern?

Headache features beyond that of ICHD-II system criteria should raise concern of a more sinister underlying cause [*Guideline*].

Causes for concern in the diagnosis of headaches may alter a diagnosis of migraine to a secondary diagnosis of headache, which can be more serious and/or life-threatening [*Guideline, Low Quality Evidence*].

Causes for concern must be evaluated irrespective of the patient's past history of headache. Warning signs of possible disorder other than primary headache are:

- Subacute and/or progressive headaches which worsen over time (months)
- A new or different headache or a statement by a headache patient that "this is the worst headache ever"
- Any headache of maximum severity at onset
- Headaches of new onset after the age of 50 years old
- Persistent headache precipitated by a Valsalva maneuver such as cough, sneeze, bending, or with exertion (physical or sexual)
- Evidence such as fever, hypertension, myalgias, weight loss, or scalp tenderness suggesting a systemic disorder
- Neurological signs that may suggest a secondary cause. For example, meningismus, confusion, altered levels of consciousness, changes or impairment of memory, papilledema, visual field defect, cranial nerve asymmetry, extremity drifts or weaknesses, clear sensory deficits, reflex asymmetry, extensor plantar response, or gait disturbances.
- Seizures

13. Consider Secondary Headache Disorder

The presence of the symptoms or signs listed above suggests a secondary cause for the headache, and could be indicative of an underlying organic condition. Alternate diagnoses include subarachnoid hemorrhage, tumor, meningitis, encephalitis, temporal arteritis, idiopathic intracranial hypertension, and cerebral venous thrombosis, among others.

Secondary Headaches

- Subacute and/or progressive, worsening headaches over weeks to months:
Headaches that worsen with time may be due to a progressive intracranial lesion such as tumor, subdural hematoma, or hydrocephalus. While the neurologic examination may reveal abnormalities that suggest a sinister process, this is not always the case. Accordingly, a history of a progressive headache is an indication for head imaging. For most processes, magnetic resonance imaging with and without gadolinium contrast will be more sensitive than a computed tomography head scan. Note: in patients who receive gadolinium contrast media used in magnetic resonance imaging (MRI), there is the potential for renal toxicity and the rare complication (3%-5% risk in patients with moderate to end-stage renal disease) of life-threatening nephrogenic systemic fibrosis. It is recommended that gadolinium use be avoided when possible in patients with advanced renal disease.
- A new or different headache or a statement by a headache patient that "this is the worst headache of my life":
Primary headache disorders (mainly tension-type headache and migraine) are exceedingly common. A history of a primary headache disorder does not confer protection against a new, serious process that presents with headache. The acuteness of a headache will largely define the differential diagnosis. Headache that presents suddenly, "like a thunderclap," can be characteristic of several serious intracranial processes, including subarachnoid hemorrhage, venous sinus thrombosis, bacterial meningitis, spontaneous cerebral spinal fluid leak, carotid dissection, and rarely, pituitary apoplexy and hypertensive encephalopathy. The first investigation is a computed tomography head scan without contrast. If there is no evidence of a subarachnoid hemorrhage, a lumbar puncture should be performed. If both studies are normal and the suspicion of subarachnoid hemorrhage is still high, MRI with and without gadolinium should be obtained. Neurological consultation is indicated and further tests for consideration include magnetic resonance angiogram and magnetic resonance venogram.

If the headache is more subacute in onset, chronic meningitis may need to be considered along with a space occupying intracranial lesion or hydrocephalus. Again, neuroimaging should be performed. Whether a lumbar puncture is done will be guided by the index of suspicion regarding a meningeal process (e.g., meningitis).
- Headache of sudden onset:
This refers mainly to thunderclap headache (see above). It should be treated as an emergency since the possible presence of aneurysmal subarachnoid hemorrhage needs to be assessed as outlined above. Other secondary causes of headache will be found less commonly.
- Headache precipitated by a Valsalva maneuver such as cough, sneeze, bending, or with exertion:
Valsalva headaches, while often representing primary cough headache, can signal an intracranial abnormality, usually of the posterior fossa. The most commonly found lesion is a Chiari malformation although other posterior fossa lesions are sometimes found. Less commonly there are intracranial lesions located elsewhere. An MRI needs to be obtained to appropriately investigate for these possibilities. Exertional headache, such as with exercise or during sexual activity, may represent a benign process such as migraine. However, if the headache is severe or thunderclap in onset, investigations will be necessary as already outlined above.
- Headaches of new onset after the age of 50 years:
The large majority of individuals who are destined to develop a primary headache disorder do so prior to age 50 years. Of course, this is not universal, and migraine or other primary headache disorders may begin even at an advanced age. Nevertheless, care should be taken before a diagnosis of a primary headache disorder is assigned. Many patients who do have the onset of a new headache disorder after age 50 years will merit brain imaging. In addition, after the age of 50 years, a new headache disorder should evoke suspicion of possible giant cell arteritis. Obviously, symptoms of polymyalgia rheumatica, jaw claudication, scalp tenderness, or fever will increase the likelihood of this diagnosis. Findings of firm, nodular temporal arteries and decreased temporal pulses will increase the suspicion as will an elevated sedimentation rate.
- Symptoms suggestive of a systemic disorder such as fever, myalgias, weight loss, or scalp tenderness or a known systemic disorder such as cancer or immune deficiency:
Systemic disorders, while not incompatible with a coexistent primary headache disorder, should signal caution. Patients should be carefully evaluated. Obviously, the differential diagnosis will be long and the index of suspicion for any given process will largely depend on the clinical setting.
- Presence of subtle neurological signs suggests a secondary cause for headache. For example, meningismus, confusion, altered level of consciousness, memory impairment, papilledema, visual field defect, cranial nerve abnormalities, pronator drift, extremity weakness, significant sensory deficits, reflex asymmetry, extensor plantar response, or gait disturbance when accompanying a headache should elicit caution:

While neurological signs may be unrelated to a headache, previously undocumented neurological findings that are presumably new need to be carefully considered. Usually cranial imaging will be the initial study. Depending on the index of suspicion, lumbar puncture and blood studies may be indicated.

- Seizures:

While seizures can occasionally be a manifestation of a primary headache disorder such as migraine, this is the exception and not the rule; it is a diagnosis of exclusion. Other etiologies for seizures including space-occupying lesions, infection, stroke, and metabolic derangements will need to be considered. Again, MRI is the imaging procedure of choice unless there is an issue of acute head trauma, in which case a computed tomography (CT) head scan should be obtained initially.

- Diagnosis to be included in secondary headache:

- Subdural hematoma
- Epidural hematoma
- Tumor
- Other metabolic disorders
- Craniocervical arterial dissection
- Giant cell arteritis
- Acute hydrocephalus
- Obstructive hydrocephalus
- Cerebral spinal fluid leaks
- Cerebral venous sinus thrombosis

This list is not intended to be all-inclusive but rather to represent the most commonly seen diagnosis for secondary headache by the primary care clinician.

14. Meets Criteria for Primary Headache Disorder?

The ICHD-II system for migraine has been studied in a community population sample without consideration of treatment. Findings suggest that the best criteria differentiating migraine from other headache types are the presence of nausea and/or vomiting in combination with two of the following three symptoms: photophobia, phonophobia, and osmophobia [Reference].

The table "Modified Diagnostic Criteria" in the original guideline document has been modified from the ICDH-II system criteria and describes the differentiating criteria applicable for the diagnosis of migraine and other primary headache disorders.

15. Evaluate Type of Primary Headache. Initiate Patient Education and Lifestyle Management

Recommendations:

- Clinicians should provide patient education and lifestyle management options to patients with headache.
- Clinicians should instruct patients with headache to maintain a diary to clarify the frequency, severity, triggers and treatment responses to their headaches.

Migraine-associated symptoms are often misdiagnosed as "sinus headache" by patients and providers. This has led to the underdiagnosis and treatment of migraine.

While education is of paramount importance in managing any condition, it is especially important in the ongoing management of headache. Patients may have to make lifestyle changes, are often required to make self-management choices in the treatment of individual headaches, and should maintain a diary to clarify the frequency, severity, triggers, and treatment responses.

Refer to the original guideline document for detailed information regarding type of headache, lifestyle changes and self-management, and for mnemonic POUNDing for the screening of migraine headache.

19. Chronic Daily Headache

Chronic daily headache refers to the presence of a headache more than 15 days per month for greater than three months. Chronic daily headache can be divided into those headaches that occur nearly daily that last four hours or less and those that last more than four hours, which is more common. The shorter-duration daily headache contains less common disorders such as chronic cluster headache and other trigeminal autonomic cephalgias. Only daily headaches of long duration are considered in this guideline.

Refer to the original guideline document for diagnostic criteria of the following types of chronic daily headache: medication-overuse headache, chronic tension-type headache, and hemicrania continua.

21. Specialty Consultation Indicated?

Recommendation:

- Clinicians may consider specialty consultation when the diagnosis or etiology cannot be confirmed, warning signals exist or quality of life is impaired.

The decision to seek a specialty consultation will depend upon the practitioner's familiarity and comfort with headache and its management. Specialty consultation may be considered when:

- The diagnosis cannot be confirmed.
- Etiology cannot be diagnosed or warning signals are present.
- Headache attacks are occurring with a frequency or duration sufficient to impair the patient's quality of life despite treatment or the patient has failed to respond to acute remedies or is in status migrainosus.

22. Perform Diagnostic Testing if Indicated

Recommendation:

- Clinicians should use a detailed headache history, that includes duration of attacks and the exclusion of secondary causes, as the principal means to diagnose primary headache. Additional testing in patients without atypical symptoms or an abnormal neurologic examination is unlikely to be helpful.

There are, as yet, no tests which confirm the diagnosis of primary headache. The diagnosis of primary headache is dependent on the clinician. The work group recommends careful consideration before proceeding with neuroimaging (CT or MRI). It is uncommon for neuroimaging to detect an abnormality in persistent headaches of longer duration versus new onset situations. Selective testing, including neuroimaging, or electroencephalogram, lumbar puncture, cerebrospinal fluid and blood studies, may be indicated to evaluate for secondary headache if causes of concern have been identified in the patient history or physical examination (see Annotation #12, "Causes for Concern?"). Diagnosis may be complicated if several headache types coexist in the same patient. The following symptoms significantly increased the odds of finding a significant abnormality on neuroimaging in patients with non-acute headache:

- Rapidly increasing headache frequency
- History of lack of coordination
- History of localized neurologic signs or a history such as subjective numbness or tingling
- History of headache causing awakening from sleep (although this can occur with migraine and cluster headache) [*Guideline*]

Refer to the original guideline document for more information.

Migraine Treatment Algorithm Annotations

27. Patient Meets Criteria for Migraine

Migraine is the most common headache disorder seen by primary care clinicians.

It is expected that a patient with headache undergo a diagnostic work-up (see the Diagnosis Algorithm) establishing the diagnosis of migraine before initiating acute treatment.

28. Is Patient Experiencing a Typical Headache?

Each individual headache must be evaluated in the context of the patient's prior migraine headaches. The practitioner must always remain alert to the possibility of secondary causes for headache, particularly when there is a previously established history of a primary headache disorder such as migraine.

Migraine headache does not preclude the presence of underlying pathology (arterial dissection, intracranial aneurysm, venous sinus thrombosis, ischemic or hemorrhagic stroke, temporal arteritis, etc.) that may also present with "vascular headaches." If the history is scrutinized, ominous causes for headaches can often be identified and treated with the potential to avoid catastrophe.

30. Categorize According to Peak Severity Based on Functional Impairment, Duration of Symptoms, and Time to Peak Impairment

Recommendations:

- Clinicians should categorize headache according to peak severity, duration of symptoms and time to peak impairment.
- Clinicians should treat according to severity.

Accurate categorization and characterization by both providers and patients is important. The categorization of migraine influences choice of treatment method.

Severity Levels

Mild - Patient is aware of a headache but is able to continue daily routine with minimal alteration.

Moderate - The headache inhibits daily activities but is not incapacitating.

Severe - The headache is incapacitating.

Status - A severe headache that has lasted more than 72 hours.

There may be additional features that influence choice of treatment. For example, parenteral administration (subcutaneous, nasal) should strongly be considered for people whose time to peak disability is less than one hour, who awaken with headache, and for those with severe nausea and vomiting.

Determining functional limitations during migraine episodes is the key to determining the severity and therefore the best treatment for a patient. Clinicians and patients should stratify treatment based on severity rather than using stepped care, though patients will often use stepped care within an attack. This algorithm uses a stratified-care model.

Factors That May Trigger Migraine

Certain influences can lead to a migraine attack. It is important to note that although a single trigger may provoke the onset of a migraine, a combination of factors is much more likely to set off an attack.

Refer to the original guideline document for a detailed list of triggers, including environmental triggers, lifestyle habits, hormonal triggers, emotional triggers, and medications.

32. Mild Treatment

Recommendations:

- Clinicians may manage mild migraines with over-the-counter medications.
- Clinicians may use triptans for mild migraine pain levels.

The guideline work group presumes most mild migraine headaches will be managed by self-care, which implies an emphasis on over-the-counter medications. However, since only 2% to 12% of initially mild migraine episodes remain mild (with the remainder progressing), treatments effective for mild headaches may be useful for only a short time. Studies on treatment of migraine headache at the mild level show that triptans are more effective in abolishing pain at this stage than if the headache is more severe. It is acceptable to use other symptomatic headache relief drugs as well as triptans for mild headache. However, current retrospective analyses of mild pain treatment studies reveal triptan response to two-hour pain freedom to be superior to any other comparator drug. Please see Appendix A, "Drug Treatment for Headache," and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document.

Use of non-steroidal anti-inflammatory drugs (NSAIDs) for acute treatment of headache for more than nine days per month or use of aspirin for more than 15 days is associated with an increased risk of chronic daily headache.

Early treatment of migraines with effective medications improves a variety of outcomes including duration, severity and associated disability [*Meta-analysis*].

Given a longer half-life of naratriptan, headache response is delayed with naratriptan when compared with other selective 5-hydroxy tryptamine (5-HT) receptor agonists. However, headache recurrence may be less frequent.

Second doses of triptans have not been shown to relieve headache more if the first dose has been ineffective.

Studies show that sumatriptan and naproxen sodium in combination may be more effective than either drug alone. However, there are no studies that demonstrate that sumatriptan 85 mg/naproxen sodium 500 mg is more effective than sumatriptan and naproxen sodium taken together. Therefore, a dose of sumatriptan 100 mg and a dose of naproxen sodium 550 mg taken at the same time is recommended.

33. Successful?

Success for treatment of migraine is defined as complete pain relief and return to normal function within two hours of taking medication. In addition, patients should not have intolerable side effects and should find their medications reliable enough to plan daily activities despite migraine headache [*Low Quality Evidence*].

Consider reasons for treatment failure and change treatment plan.

Common reasons for migraine treatment failure are provided in the original guideline document.

36. Moderate Treatment

Recommendation:

- Clinicians should avoid the use of opiates and barbiturates in the treatment of headache.

Early treatment of migraines with effective medications improves a variety of outcomes including duration, severity, and associated disability [*Meta-analysis*].

The use of opiates and barbiturates should be avoided. This guideline emphasizes the use of other agents over opiates and barbiturates, recognizing that many migraineurs are currently treated with drugs from the latter two classes. In general, opiates are characterized by having a short pain-relief window, release inflammatory neurochemicals, and increase vasodilation; none of these addresses the currently known treatment issues and pathophysiology of migraine.

Meperidine should be avoided. The metabolite of meperidine, normeperidine, has a long half-life, produces less analgesic effect, and there is an increased risk of seizures that cannot be reversed by naloxone. The guideline developers have specifically excluded butorphanol because of its high potential for abuse and adverse side-effect profile.

If an opiate must be used, meperidine should not be the opiate selected.

See Appendix A, "Drug Treatment for Headache" and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document.

43. Status (Greater Than 72 Hour Duration)

Recommendation:

- It is recommended that the patient be hydrated prior to neuroleptic administration with 250-500 mL of 5% dextrose with 0.45% sodium chloride intravenously and advised of the potential for orthostatic hypotension and acute extrapyramidal side effects. The patient should be observed in a medical setting as clinically appropriate after administration of a neuroleptic and should not drive for 24 hours.

44. Adjunctive Therapy

Recommendation:

- Clinicians may consider adjunctive therapy as a treatment option for headache.

See Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document. As adjunctive therapy, any of the listed medications can be used singularly or in compatible combination. For intermittent, infrequent headache, caffeine should be added as first choice when not contraindicated. The use of caffeine in patients with chronic daily headache is to be discouraged. The prokinetic agent metoclopramide could be considered next. This guideline has no other preferences.

45. Patient Meets Criteria for Dihydroergotamine Mesylate (DHE)?

DHE is effective in halting intractable migraine attacks or migraine status. DHE is also effective in halting the acute cycle of cluster headaches.

DHE must not be given to patients with the following conditions:

- Pregnancy and breastfeeding
- History of ischemic heart disease
- History of Prinzmetal's angina
- Severe peripheral vascular disease
- Onset of chest pain following administration of test dose
- Within 24 hours of receiving any triptan or ergot derivative
- Elevated blood pressure
- Patients with hemiplegic or basilar-type migraine (basilar-type migraine is defined as three of the following features: diplopia, dysarthria, tinnitus, vertigo, transient hearing loss or mental confusion) [*Guideline*]
- Cerebrovascular disease

Intravenous DHE is the method most frequently employed to terminate a truly intractable migraine attack or migraine status. The protocol outlined in the DHE algorithm is effective in eliminating an intractable migraine headache in up to 90% of patients within 48 hours. This method of administration has also been found to be effective in terminating an acute cycle of cluster headaches as well as chronic daily headaches with or without analgesic/ergotamine rebound.

47. Chlorpromazine, Intravenous Valproate Sodium, Intravenous Magnesium Sulfate or Prochlorperazine

Recommendations:

- Clinicians should treat patients with migraine >72 hours who do not meet criteria for DHE with chlorpromazine, intravenous valproate sodium, intravenous magnesium sulfate or prochlorperazine.
- Clinicians should premedicate patients with diphenhydramine or benztropine who have migraine for >72 hours who do not meet criteria for DHE and who have a history of dystonic reaction.

See Appendix A, "Drug Treatment for Headache" and Appendix B, "Drug Treatment for Adjunctive Therapy" in the original guideline document.

If chlorpromazine, valproate sodium, or intravenous magnesium sulfate was used previously, one may not wish to repeat.

49. Opiates

These are not drugs of first choice and headache practice recommends against the use of meperidine. Normeperidine, the active metabolite of meperidine, has a long half-life and is neuroexcitatory and neurotoxic. There is inconsistent absorption of opiates, at least with meperidine, when injected intramuscularly, and they are less effective than when given intravenously. Opiates release inflammatory neurochemicals and increase vasodilation that are mechanistically counterproductive to currently known migraine pathophysiology and can exacerbate headaches. Studies have been done using meperidine but the effects are likely due to class effect and other opiates are likely to be just as effective [*High Quality Evidence*]. However, it should be noted that there are no studies to support opiate effectiveness.

See Appendix A, "Drug Treatment for Headache," and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document.

51. Dexamethasone

See Appendix A, "Drug Treatment for Headache," and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document.

Migraine Treatment - Annotations #32, 36, 39, 44, 47, 49, 51

Adolescents

At this time the majority of the adolescent literature supports a strong placebo effect in this age group. Success of triptans and prophylactic medications in patients age 12-17 yield similar positive outcomes as in adult studies, but placebo administered in blinded, controlled studies has a similar effect. There has been a recent study that supports the use of almotriptan with statistically significant efficacy over placebo. As an acute treatment, almotriptan in the dose of 12.5 mg was effective in relieving pain and associated symptoms and was well tolerated [*High Quality Evidence*].

See Appendix A, "Drug Treatment for Headache," in the original guideline document for more information.

Tension-Type Headache Algorithm Annotations

59. Patient Meets Criteria for Tension-Type Headache?

Tension-type headache is one of the most common primary headaches. See Annotation #14 "Meets Criteria for Primary Headache Disorder?" for episodic (less than 15 days per month) and chronic tension-type headache (more than 15 days per month).

It is important to evaluate the patient who comes to the office for tension-type headache for the possibility of migraine. While the ICHD-II system suggests migraine and tension-type headaches are distinct disorders, there is evidence to suggest that for the migraineur, tension-type headache is actually a low-intensity migraine [*High Quality Evidence*], [*Low Quality Evidence*].

62. Acute Treatment

Recommendation:

- Clinicians may utilize over-the-counter analgesics or prescription NSAIDs for tension-type headache treatment.

Analgesics offer a simple and immediate relief for tension-type headache. Medication overuse is potentially a concern that can lead to chronic daily headache. Use of drugs for acute treatment of headache for more than nine days per month is associated with an increased risk of chronic daily headache.

See Appendix A, "Drug Treatment for Headache," and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document.

[High Quality Evidence], [Low Quality Evidence]

Electromyography biofeedback has been found to have an effect on tension-type headaches. The goal is to help patients recognize muscle tension. Fifty-three studies have shown medium to large effect *[Guideline]*.

66. Prophylactic Treatment

Recommendation:

- Prophylactic treatment, including the use of tricyclic antidepressants, may be used for chronic tension-type headaches.

Prophylactic therapy is reserved for patients with chronic tension-type headache (more than 15 headaches per month).

Tricyclic antidepressants are effective in reducing the frequency and severity of tension-type headache.

[High Quality Evidence], [Low Quality Evidence]

Cluster Headache Algorithm Annotations

71. Patient Meets Criteria for Cluster Headache?

There is no more severe pain than that sustained by a cluster headache sufferer. This headache is often termed "suicide headache." Cluster headache is characterized by repeated short-lasting but excruciating intense attacks of strictly unilateral peri-orbital pain associated with local autonomic symptoms or signs. The most striking feature of cluster headache is the unmistakable circadian and circannual periodicity. Many patients typically suffer daily (or nightly) from one or more attacks over a period of weeks or months *[Low Quality Evidence]*, *[High Quality Evidence]*.

75. Acute Treatment

Recommendations:

- Clinicians should utilize inhaled oxygen for the treatment of cluster headaches at a rate of 7-15 L/min.
- Clinicians should consider using subcutaneous sumatriptan or intranasal zolmitriptan as a first line option for the treatment of cluster headaches.

Oxygen inhalation is highly effective when delivered at the beginning of an attack with a non-rebreathing facial mask (7-15 L/min). Most patients will obtain relief within 15 minutes. Acute drugs may be difficult to obtain in adequate quantity.

Subcutaneous sumatriptan and intranasal zolmitriptan are the most effective self-administered medication for the relief of cluster headaches. Sumatriptan is not effective when used before the actual attack nor is it useful as a prophylactic medication *[Systematic Review]*. Intranasal sumatriptan can also be considered for acute treatment *[Moderate Quality Evidence]*.

DHE provides prompt and effective relief from cluster headaches in 15 minutes, but due to the rapid peak intensity and short duration of cluster headaches, DHE may be a less feasible option than sumatriptan.

See Appendix A, "Drug Treatment for Headache," and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document.

[Low Quality Evidence], [High Quality Evidence]

76. Bridging Treatment

Recommendation:

- Clinicians should initiate bridging treatment or transitional prophylaxis simultaneously with maintenance prophylactic treatment after acute treatment has suppressed the initial attack for cluster headaches.

Bridging treatment allows for the rapid suppression of cluster attacks in the interim until the maintenance treatment reaches therapeutic levels.

Options for bridging treatment are:

- Corticosteroids
- Occipital nerve block

[Guideline], [Low Quality Evidence], [High Quality Evidence]

77. Maintenance Prophylaxis

Recommendation:

- Clinicians should initiate maintenance prophylaxis to provide sustained suppression of cluster headaches over the expected cluster period.

Effective prevention cannot be overemphasized in these patients. Maintenance prophylaxis is critically important since cluster headache sufferers typically experience one or more daily (or nightly) attacks for a period of weeks or months. The goal of transitional therapy is to induce rapid suppression of attacks while maintenance prophylaxis is intended to provide sustained suppression over the expected cluster period.

If the patient has intractable headache or is unresponsive to prophylactic treatment, consider referral to a headache specialist.

See Appendix A, "Drug Treatment for Headache," and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document.

[Low Quality Evidence], [Reference], [High Quality Evidence]

Dihydroergotamine Mesylate (DHE) Algorithm Annotations

84. Intravenous Metoclopramide 10 mg

Metoclopramide (10 mg) is given either by direct intravenous injection over 2-3 minutes, or infused intravenously in 50 mL of normal saline over 15 minutes. Each dose of metoclopramide should be administered 15 minutes prior to each DHE injection. Although uncommon, acute extrapyramidal side effects such as dystonia, akathisia, and oculogyric crisis may occur after administration of metoclopramide. Benztropine mesylate is effective in terminating this unusual adverse event, given as a 1-mg injection (intravenous or intramuscular). Often after five doses of metoclopramide, it may be given as needed every eight hours for nausea *[High Quality Evidence]*.

85. Begin Continuous DHE

Begin DHE 2 mg in 1,000 mL normal saline at 42 mL/hr. Limit the dose of DHE to no more than 2 mg/24 hours.

Continue intravenous metoclopramide 10 mg IV every eight hours as needed for nausea.

Side Effects

- If significant nausea occurs at any time, reduce the rate of DHE to 21 to 30 mL/hr.
- If diarrhea occurs, give diphenoxylate with atropine, one or two tablets, three times daily as needed.
- If excessive anxiety, jitteriness (akathisia), or dystonic reaction occurs, give intravenous benztropine 1 mg.

It may be continued up to seven days.

This approach is an alternative to the intermittent dosing of DHE as outlined in the Raskin protocol, and some practitioners may prefer it rather than the intermittent DHE protocol. Continuous DHE, like the intermittent administration, can be continued for seven days, although 72 hours is more typical. Opioid analgesics should not be used with either protocol since these are likely to prolong the headache via analgesic rebound.

Menstrual-Associated Migraine Algorithm Annotations

87. Patient Meets Criteria for Menstrual Only or Menstrual-Associated Migraine

Recommendation:

- Clinicians should advise women who meet criteria for menstrual-associated migraine to keep a continuous daily record of headache occurrence, severity, duration and menstrual flow for at least two months.

"Menstrual migraine," a term misused by both patients and clinicians, lacks precise definition. The ICHD-II system has proposed that menstrual-only migraine be defined as attacks exclusively starting two days before and first two days of the menstrual cycle *[Meta-analysis], [Guideline]*. The woman should be free from attacks at all other times of the cycle.

Many women who do not have attacks exclusively with menses are considered to have menstrual-associated migraines *[Low Quality Evidence]*.

The clinician and patient need to discuss diary documentation. The patient should keep a continuous daily record for at least two months to include the following:

- Day/time of headache
- Severity of headache
- Duration

- Onset of menstrual flow

91. Consider Cyclic Prophylaxis

Recommendations:

- Clinicians may consider non-hormonal cyclic prophylactic treatment with NSAIDs and triptans for patients with menstrual-associated migraine.
- NSAIDs

NSAIDs should be considered approaches of first choice in the prophylactic treatment of migraine associated with menses. Many clinicians consider triptans to be equally effective, but there are no comparative studies. [*Conclusion Grade III: See Conclusion Grading Worksheet A -- Annotation #91 (Non-Steroidal Anti-Inflammatory Drugs) in the original guideline document*].

Naproxen sodium has been used as a preventive agent, although other NSAIDs may also be effective. Typically, the agent is initiated 2 to 3 days before anticipated onset of the headache and continued through the at-risk period.

- Triptans

There are good placebo studies supporting the use of triptans (sumatriptan, naratriptan, frovatriptan and zolmitriptan) for cyclic prophylaxis [*High Quality Evidence*], [*Low Quality Evidence*].

94. Consider Hormone Prophylaxis

Recommendations:

- Clinicians may consider hormone prophylaxis treatment for patients with menstrual-associated migraines.
- Transdermal Estradiol

Estrogen levels decrease during the late luteal phase of the menstrual cycle, likely triggering migraine. Estrogen replacement prior to menstruation has been used to prevent migraine.

Estradiol patches, 50-100 µg, are applied 48 hours prior to expected onset of migraine and used for one week.

[*Low Quality Evidence*]

- Estrogen-Containing Contraceptives

Estrogen-containing contraceptives have a variable effect on migraines, causing worsening of headaches in some patients, improvement of headaches in a small percentage of patients, and no change in migraines in other patients. The guideline developers are not aware of any population-based studies on this topic.

[*Low Quality Evidence*]

In a contraceptive containing drospirenone, an extended 168-day placebo-free oral contraceptive regimen showed a significant decrease in duration, severity of headaches, and loss of function due to headache compared with a standard 21/7 oral contraceptive cycle [*Low Quality Evidence*]. In 2011, the Food and Drug Administration concluded that drospirenone may be associated with a higher risk for blood clots than other progestin-containing pills (<http://www.fda.gov/Drugs/DrugSafety/ucm273021.htm>).

- Gonadotropin-Releasing Hormone (GnRH) Agonists with "Add Back" Therapy

For patients with severe menstrual migraine unrelieved by other therapies, suppression of the menstrual cycle with a gonadotropin-releasing hormone agonist and "add back" therapy may be effective.

Tamoxifen, danazol and bromocriptine have shown limited efficacy in treatment of menstrual migraine.

Whether oophorectomy is an effective treatment for refractory migraines is not settled at this time.

[*Low Quality Evidence*]

Perimenopausal or Menopausal Migraine Algorithm Annotations

98. Perimenopausal or Menopausal with Active Migraine History and Is a Potential Candidate for Hormone Therapy

Recommendation:

- Clinicians should not prescribe hormone therapy for perimenopausal or menopausal migraine treatment in patients who are pregnant or have unexplained bleeding.

Menopause is the permanent cessation of menses.

Perimenopause is the span of time from the reproductive to the post-reproductive interval.

Hormone therapy may worsen, improve, or leave migraines unchanged.

[Low Quality Evidence], [High Quality Evidence]

Women with these conditions are not candidates for hormone therapy:

- Pregnancy or unexplained bleeding: these are temporary but absolute contraindications to hormone therapy.
- Past history of breast cancer or endometrial cancer: while usually considered contraindications to hormone therapy, short-term use for severe menopausal symptoms may be considered with proper precautions.

103. Hormone Therapy

- Transdermal, transvaginal or oral estrogen
- Progestin if indicated
- Estrogen-containing contraceptives

[Low Quality Evidence]

104. Successful?

Successful is commonly defined as a 50% reduction in frequency in headache days and/or severity of headaches.

On Estrogen-Containing Contraceptives or Considering Estrogen-Containing Contraceptives with Migraine Algorithm Annotations

109. On Estrogen-Containing Contraceptives or Considering Estrogen-Containing Contraceptives with Migraine

Migraine patients who do not have absolute contraindications to estrogen-containing contraceptives should consider that estrogen-containing contraceptives may have unpredictable effects on the severity and/or frequency of headaches. In addition, evidence exists that the risk of ischemic stroke increases for migraineurs taking estrogen-containing contraceptives *[Guideline], [Low Quality Evidence]*.

111. Evaluate Vascular Risk Factors

Recommendation:

- Clinicians should evaluate for vascular risk factors before prescribing estrogen containing contraceptives for treatment of migraine.
- Risk factors for coronary artery disease
- Prior thromboembolic disease
- Migraine aura
- Smoking

Women who have migraine with an aura probably have significantly increased ischemic stroke risk if estrogen-containing contraceptives are used. This risk probably increases with age as baseline stroke rates increase, so that the increased risk may be acceptable to the younger patient (i.e., under age 30), but not to the older patient. It is probably too simplistic to say that no patient with migraine with aura should use estrogen-containing contraceptives. The decision should be individualized and should be made with the patient.

It appears reasonable that women who have prolonged migraine auras (certainly those beyond 60 minutes), multiple aura symptoms, or less common aura symptoms (i.e., dysphasia, hemiparesis) should be strongly discouraged from using estrogen-containing contraceptives.

Patients who develop a migraine aura for the first time while using estrogen-containing contraceptives, or whose previous typical migraine aura becomes more prolonged or complex, should discontinue estrogen-containing contraceptives.

Use of oral contraceptives in patients with a history of migraine increases the risk of stroke *[Conclusion Grade II: See Conclusion Grading Worksheet B - Annotation #111 (Risk of Stroke) in the original guideline document]*

Women with migraine aura who smoke and are hypertensive further increase their risk. Additional risk is also noted if they are taking estrogen-containing contraceptives.

Migraine Prophylactic Treatment Algorithm Annotations

122. Prophylactic Treatment

Recommendation:

- Clinicians may prescribe prophylactic treatment for patients with migraine history after realistic goals and expectations have been established with the patient.

- Criteria for Prophylactic Treatment

- Three or more severe migraine attacks per month that fail to respond adequately to symptomatic therapy.
- Less frequent but protracted attacks that impair the patient's quality of life.
- Patient is interested in prophylactic treatment.

- Prophylactic Therapy

Prior to instituting prophylactic therapy for migraine, it is imperative that realistic goals and expectations be established. Patients should have a clear understanding that the goals of preventative therapy are to:

- Decrease migraine attack frequency by 50% or more
- Decrease pain and disability with each individual attack
- Enhance response to acute, specific, anti-migraine therapy

One or more of these goals may be achieved.

- Medications

The choice of prophylactic agent depends upon:

- Side effect profile
- Comorbid conditions
- Medication interactions
- Evidence-based efficacy
- Patient preference (weight loss or gain)

Patients should also understand that there is usually a latency of at least 3 to 6 weeks between the initiation of medication and recognizable efficacy. Often, an 8- to 12-week trial is necessary, allowing an adequate period for drug titration to a dosage likely to attain efficacy. It is also not uncommon for initial side effects to subside after continued therapy, and patients should be made aware of this so as to avoid premature discontinuation of a potentially effective medication.

The choice of prophylactic medication should be individualized according to the side effect profile, the presence of comorbid conditions, and risk of medication interactions. For example, a tricyclic antidepressant may be especially useful with a migraineur with depression, while sodium valproate may be ideal for a patient with epilepsy.

Reinforce education and lifestyle management. Refer to Annotation #15, "Evaluate Type of Primary Headache. Initiate Patient Education and Lifestyle Management."

- Adolescents

As a prophylactic treatment topiramate 100 mg/day was effective in reduction of the number of migraine headaches a month [*High Quality Evidence*].

Refer to the original guideline document for references pertaining to the medications used in prophylactic treatment (antiepileptics, beta-blockers, calcium channel blockers, tricyclics).

Other Therapies

The treatment therapies listed below are in alphabetical order and do not indicate work group preference or scientific support.

- Acupuncture

A systematic (Cochrane) review of acupuncture in migraine prophylaxis demonstrated that adding acupuncture to patients getting only acute treatment for headaches reduced the number of headaches patients had. When true and sham acupuncture were compared, they both reduced the number of headaches. There was no difference in benefit between true and sham acupuncture groups when results for all trials were pooled. Acupuncture demonstrated slightly better outcomes and fewer adverse effects than drugs shown to be helpful for prophylaxis [*Systematic Review*].

- Biofeedback

Various methods of biofeedback have been used as adjunctive therapy for migraine and tension-type headaches. A meta-analysis of 53 studies of biofeedback in combination with relaxation for tension-type headache demonstrated these to be more effective than

headache monitoring, placebo or relaxation, especially in reducing headache frequency. Most of these studies were randomized controlled trials. Effects were most pronounced in adolescents [*Meta-analysis*].

- Butterbur Root (*Petasites hybridus*)

An extract from the plant *Petasites hybridus* is effective for migraine prevention. It should be used to reduce severity and frequency of migraine attacks [*Guideline*], [*Moderate Quality Evidence*], [*High Quality Evidence*].

- Coenzyme Q10

In one randomized placebo-controlled trial, coenzyme Q10 was superior to placebo for attack frequency, headache days and days with nausea [*High Quality Evidence*].

- Cognitive Behavioral Therapy

This therapy is based on the premise that anxiety and distress aggravate an evolving migraine, and it has the potential for helping the patient recognize maladaptive responses that may trigger a headache [*Guideline*], [*Low Quality Evidence*].

Psychological treatments, principally relaxation and cognitive behavioral therapies, are effective treatments of childhood headache [*Meta-analysis/Systematic Review*].

- Feverfew

This herbal therapy is made from crushed chrysanthemum leaves. 250 µg of the active ingredient, parthenolide, is considered necessary for therapeutic effectiveness. Because these are herbal preparations, the quantity of active ingredient varies with the producer [*Systematic Review*], [*High Quality Evidence*].

- Magnesium

Daily oral dosages of 400 to 600 mg of this salt have been shown to be of benefit to migraineurs in European studies [*High Quality Evidence*].

- Onabotulinum Toxin

Onabotulinum toxin has been approved by the Food and Drug Administration for the treatment of chronic migraine. Since this approach would be used by headache specialists or others trained specifically for use of this product, onabotulinum toxin is beyond the scope of this discussion.

- Physical Therapy

Individuals unable to take medication or interested in other nonpharmacological headache management, may benefit from physical therapy including craniocervical exercises. Craniocervical exercises designed to correct postural faults by retraining and strengthening craniocervical flexion, cervico-thoracic extension, scapular retraction, thoracic extension and normalization of lumbar lordosis have been shown to significantly reduce tension-type and cervicogenic headaches over a prolonged time frame [*High Quality Evidence*].

- Relaxation Training

Relaxation training includes progressive muscular relaxation, breathing exercises, and directed imagery. The goal is to develop long-term skills rather than to treat individual events. Repetitive sessions and practice by the patient increase the success of these therapies in reducing headache frequency [*High Quality Evidence*].

- Riboflavin

A randomized, placebo-controlled study has found daily supplements of 400 mg moderately effective in reducing the frequency and severity of migraine [*High Quality Evidence*].

Several additional treatment modalities are available. The modalities listed below lack sufficient scientific support to be recommended as therapies of proven value.

- Cervical Manipulation

Previous studies suggested potentially high levels of risk associated with improper application of this modality. Although some studies report few complications, the scientific evidence of significant benefit is not convincing. There is well-documented evidence of cerebral infarction and death from cervical manipulation [*Low Quality Evidence*], [*High Quality Evidence*]. A systematic review demonstrates that numerous deaths have been associated with high-velocity, short-lever thrusts of the upper spine with rotation [*Meta-analysis*].

- Transcutaneous Electrical Stimulation Units

Transcutaneous electrical stimulation units for migraine or muscle contraction headache have not been found to be more beneficial

than placebo when evaluated in a controlled study [*High Quality Evidence*].

124. Continue Treatment for 6-12 Months, Then Reassess

Recommendation:

- After 6 to 12 months, a gradual taper of prophylactic migraine treatment is recommended unless headaches become more frequent or more severe.

125. Try Different First-Line Medication or Different Drug of Different Class

Recommendation:

- Monotherapy is recommended with dose increasing until patient receives benefit, maximum recommended dose is reached, or unacceptable side effects occur. If failure with one medication, try another from the same class.

128. Try Combination of Beta-Blockers and Tricyclics

A beta-blocker and a tricyclic antidepressant may be more effective and produce fewer side effects in combination than a single drug at a higher dose from either class.

Definitions:

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below and are assigned a designator of +, -, or Ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Conclusion Grades

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations

The symbols +, -, Ø and N/A found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

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Following a review of several evidence rating and recommendation writing systems, the Institute for Clinical System Improvement (ICSI) has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Crosswalk between ICSI Evidence Grading System and GRADE

ICSI GRADE System		Previous ICSI System
High, if no limitation	Class A:	Randomized, controlled trial
Low	Class B:	[observational]
		Cohort study
	Class C:	[observational]
		Non-randomized trial with concurrent or historical controls
Low		Case-control study
Low		Population-based descriptive study
*Low		Study of sensitivity and specificity of a diagnostic test
*Following individual study review, may be elevated to Moderate or High depending upon study design		
	Class D:	[observational]
Low		Cross-sectional study
		Case series
		Case report
Meta-analysis	Class M:	Meta-analysis
Systematic Review		Systematic review
Decision Analysis		Decision analysis
Cost-Effectiveness Analysis		Cost-effectiveness analysis
Low	Class R:	Consensus statement
Low		Consensus report
Low		Narrative review
Guideline	Class R:	Guideline
Low	Class X:	Medical opinion

Evidence Definitions

High Quality Evidence = Further research is very unlikely to change confidence in the estimate of effect.

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Low Quality Evidence = Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate or any estimate of effect is very uncertain.

In addition to evidence that is graded and used to formulate recommendations, additional pieces of literature will be used to inform the reader of other topics of interest. This literature is not given an evidence grade and is instead identified as a Reference throughout the document.

Clinical Algorithm(s)

Detailed and annotated clinical algorithms are provided in the original guideline document (see the "Guideline Availability" field) for:

- Diagnosis and Treatment of Headache (main algorithm)
- Diagnosis
- Migraine Treatment
- Tension-Type Headache
- Cluster Headache
- Dihydroergotamine Mesylate (DHE)
- Menstrual-Associated Migraine
- Perimenopausal or Menopausal Migraine
- On Estrogen-Containing Contraceptives or Considering Estrogen-Containing Contraceptives with Migraine
- Migraine Prophylactic Treatment

Scope

Disease/Condition(s)

- Migraine headache (including hormone-related migraine such as menstrual-associated migraine, perimenopausal or menopausal migraine, and on estrogen-containing contraceptives migraine)
- Tension-type headache
- Cluster headache

Note: This guideline does not specifically address occipital neuralgia.

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Obstetrics and Gynecology

Pediatrics

Pharmacology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To increase the accurate diagnosis of primary headaches in patients age 12 years and older
- To increase the percentage of patients with primary headache diagnosis who receive educational materials about headache
- To increase the percentage of patients with primary headache syndrome who receive prophylactic treatment
- To increase the percentage of patients with migraine headache who have improvement in their functional status
- To increase the percentage of patients with migraine headache who have a treatment plan or report adherence to a treatment plan
- To decrease the percentage of patients with migraine headache who are prescribed opiates and barbiturates for the treatment of migraines to less than 5%
- To increase the percentage of patients with migraine headache who have appropriate acute treatment

Target Population

Patients age 12 years and older who present with headache

Note: For the purpose of this guideline, pain that primarily involves the back of the neck and only involves the head to a limited extent is not considered a headache.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Detailed history of headaches, including a focused physical and neurological exam
2. Evaluation of causes for concern
3. Consider secondary headache disorder (e.g., hematoma, metabolic disorder, hydrocephalus)
4. Evaluation of type of primary headache
5. Patient education and lifestyle management
6. Specialty referral as indicated
7. Diagnostic testing if indicated

Treatment/Management

1. Over-the-counter medications
2. Triptans
3. Adjunctive therapy, including caffeine and metoclopramide
4. Dihydroergotamine mesylate (DHE)
5. Chlorpromazine, intravenous valproate sodium, intravenous magnesium sulfate, or prochlorperazine
6. Opiates
7. Dexamethasone
8. Inhaled oxygen
9. Bridging treatment
 - Corticosteroids

- Occipital nerve block
- 10. Hormone therapy
- 11. Prophylactic treatment
 - Cyclic prophylaxis
 - Hormone prophylaxis
 - Antiepileptics
 - Beta-blockers
 - Calcium channel blockers
 - Tricyclic antidepressants
- 12. Screening for depression and anxiety
- 13. Referral to specialist
- 14. Other therapies (e.g., acupuncture, biofeedback, butterbur root, coenzyme Q10, cognitive behavioral therapy, feverfew, magnesium, onabotulinum toxin, physical therapy, relaxation therapy, riboflavin)

Major Outcomes Considered

- Accuracy of diagnostic assessments and diagnostic yield
- Functional status and quality of life
- Headache frequency and severity
- Risk of stroke with oral contraceptive use
- Safety, cost, and side effects of medications

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A consistent and defined process is used for literature search and review for the development and revision of Institute for Clinical Systems Improvement (ICSI) guidelines. The literature search was divided into two stages to identify systematic reviews (stage I), and randomized controlled trials, meta-analyses and other literature (stage II). Literature search terms used for this revision are below and include diagnosis of headache, migraine treatment, tension-type headache treatment, cluster headache treatment, menstrual-associated migraine treatment, perimenopause or menopause migraine treatment, pharmacologic treatment of headache, Botox and headache in PubMed from June 2010 through July 2012.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

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ICSI GRADE System	Previous ICSI System	Case series
		Case report
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Systematic Review		Systematic review
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Cost-Effectiveness Analysis		Cost-effectiveness analysis
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Low		Consensus report
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In addition to evidence that is graded and used to formulate recommendations, additional pieces of literature will be used to inform the reader of other topics of interest. This literature is not given an evidence grade and is instead identified as a Reference throughout the document.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

New Guideline Development Process

A work group consisting of 6 to 12 members that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, and an Institute for Clinical Systems Improvement (ICSI) staff facilitator develops each document. Ordinarily, one of the physicians will be the leader.

Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 members may be recruited from medical groups, hospitals, or other organizations that are not members of ICSI. Patients on occasion are invited to serve on work groups.

The work group will meet for 7 to 8 three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and footnotes and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

Revision Process of Existing Guidelines

ICSI scientific documents are revised every 12 to 24 months as indicated by changes in clinical practice and literature. For documents that are revised on a 24-month schedule, ICSI checks with the work group on an annual basis to determine if there have been changes in the literature significant enough to cause the document to be revised earlier or later than scheduled. For yearly reviewed documents, ICSI checks with every work group 6 months before the scheduled revision to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Literature Search

ICSI staff, working with the work group to identify any new pertinent clinical trials, systematic reviews, or regulatory statements and other professional guidelines, conduct a literature search.

Revision

The work group will meet for 1 to 2 three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

A second review by members is indicated if there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations. If a review by members is not needed, the document goes to the appropriate steering committee for approval according to the criteria outlined above.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

- Reducing office visits, emergency department visits, and inpatient admissions for uncontrolled headache syndromes along with reducing unnecessary tests and procedures for headache diagnosis is likely to reduce total costs of care even if there are more visits for diagnosis of headache and increased costs for headache-specific drugs.
- In a retrospective study, 592 patients with headaches and normal neurological exam were examined by computed tomography (CT) scanning between 1990 and 1993 at a cost of \$1,000 per scan. None of the patients had any serious intracranial pathology identified. This technique is costly and unrewarding.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Critical Review Process

The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes necessary across systems in their organization to implement the

guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within the Institute for Clinical Systems Improvement (ICSI).

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Document Approval

Each document is approved by the Committee for Evidence-Based Practice (CEBP).

The committee will review and approve each guideline/protocol, based on the following criteria:

- The aim(s) of the document is clearly and specifically described.
- The need for and importance of the document is clearly stated.
- The work group included individuals from all relevant professional groups and had the needed expertise.
- Patient views and preferences were sought and included.
- The work group has responded to all feedback and criticisms reasonably.
- Potential conflicts of interest were disclosed and do not detract from the quality of the document
- Systematic methods were used to search for the evidence to assure completeness and currency.
- Health benefits, side effects, risks and patient preferences have been considered in formulating recommendations.
- The link between the recommendation and supporting evidence is clear.
- Where the evidence has not been well established, recommendations based on community practice or expert opinion are clearly identified.
- Recommendations are specific and unambiguous.
- Different options for clinical management are clearly presented.
- Clinical highlights and recommendations are easily identifiable.
- Implementation recommendations identify key strategies for *health care systems* to support implementation of the document.
- The document is supported with practical and useful tools to ease *clinician* implementation.
- Where local resource availability may vary, alternative recommendations are clear.
- Suggested measures are clear and useful for quality/process improvement efforts.

Once the document has been approved, it is posted on the ICSI Web site and released to members for use.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and treatment of headache, leading to the prevention of or reduction in symptoms and improvement in functional status and improved health of the population

Potential Harms

Side Effects of Medication

- Use of drugs for acute treatment of headache for more than 9 days per month is associated with an increased risk of chronic daily headaches.
- In patients who receive gadolinium contrast media used in magnetic resonance imaging (MRI), there is the potential for renal toxicity and the rare complication (3%-5% risk in patients with moderate to end-stage renal disease) of life-threatening nephrogenic systemic fibrosis. It is recommended that gadolinium use be avoided when possible in patients with advanced renal disease.
- Dihydroergotamine mesylate (DHE) is associated with nausea, diarrhea, excessive anxiety, jitteriness (akathisia), and dystonic reaction.
- The effect of estrogen-containing contraceptives on migraines is unpredictable. Evidence exists that the risk of ischemic stroke increases for migraineurs using estrogen-containing contraceptives.
- Gonadotropin-releasing hormone (GnRH) agonists and "add back" therapy may be associated with erratic bleeding.
- Although uncommon, acute extrapyramidal side effects such as dystonia, akathisia, and oculogyric crisis may occur after administration of metoclopramide. Benztropine mesylate is effective in terminating this unusual adverse event, given as a 1 mg injection (intravenous or intramuscular).
- In 2011, the Food and Drug Administration concluded that drospirenone may be associated with a higher risk for blood clots than other progestin-containing pills.

Refer to Appendix A, "Drug Treatment for Headache," and Appendix B, "Drug Treatment for Adjunctive Therapy," in the original guideline document for a list of side effects of recommended drugs.

Contraindications

Contraindications

- Dihydroergotamine mesylate must not be given to or continued in patients who develop the following conditions:
 - Pregnancy
 - History of ischemic heart disease
 - History of Prinzmetal's angina
 - Severe peripheral vascular disease
 - Onset of chest pain following administration of test dose
 - Within 24 hours of receiving any triptan or ergot derivative
 - Elevated blood pressure
 - Patients with hemiplegic or basilar-type migraines (basilar-type migraine is defined as three of the following features: diplopia, dysarthria, tinnitus, vertigo, transient hearing loss or mental confusion.)
 - Cerebrovascular disease
- Women with these conditions are not candidates for hormone therapy:
 - Pregnancy or unexplained bleeding: these are temporary but absolute contraindications to hormone therapy.
 - Past history of breast cancer or endometrial cancer: while usually considered contraindications to hormone therapy, short-term use for severe menopausal symptoms may be considered with proper precautions.

Refer to Appendix A, "Drug Treatment for Headache," and Appendix B, "Prophylactic Treatment," in the original guideline document for a detailed list of contraindications to recommended drugs.

Qualifying Statements

Qualifying Statements

- The information contained in this Institute for Clinical Systems Improvement (ICSI) Health Care Guideline is intended primarily for health professionals and other expert audiences.
- This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients and families are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI Health Care

Guideline and applying it in their individual case.

- This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition.
- This guideline discusses headache disorders most commonly seen in primary care offices. It is not a comprehensive discussion of diagnosis and treatment of all headache syndromes, since many headaches are rare and felt best treated by headache specialists or neurologists with specialization in headache. It is intended for primary care clinicians to help with their diagnosis and treatment of four main types of headache: migraine, tension-type headache, cluster headache and chronic daily headache. This guideline is necessarily long and may be considered by some to be cumbersome. However, extensive information pertaining to headaches is covered, along with the typical medications. As there are multiple easy-to-access information sources available containing current detailed drug information, drug tables in the appendices highlight only selected drugs whose dosing, side effects and contraindications might otherwise be challenging to locate.

Implementation of the Guideline

Description of Implementation Strategy

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design
- Training and education
- Culture and the need to shift values, beliefs and behaviors of the organization

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline:

- Develop a system for assessment of headache based on history and functional impairment.
- Develop a system for results of this assessment to be used for identification of treatment options/recommendations.
- Develop systems that allow for consistent documentation and monitoring based on type of headache.
- Develop a system for follow-up assessment that identifies success in management of headache in the primary care setting.
- Develop a process that will remove barriers to referral to a specialist if indicated.
- Develop a system for consistent documentation and monitoring of medication administration.

Implementation Tools

Clinical Algorithm

Quality Measures

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents and Patient Resources* fields below.

Related NQMC Measures

Diagnosis and treatment of headache: percentage of patients diagnosed with primary headache using the appropriate diagnostic criteria.

Diagnosis and treatment of headache: percentage of patients with a primary headache who received educational materials on headache.

Diagnosis and treatment of headache: percentage of patients with primary headache syndrome who are prescribed prophylactic treatment when appropriate.

Diagnosis and treatment of headache: percentage of patients with migraine headache who are showing improvement in functional status shown by using one of the following disease-specific tools or questionnaires (e.g., MIDAS, Headache Impact Test [HIT], Migraine Specific Quality of Life [MSQ]).

Diagnosis and treatment of headache: percentage of patients with migraine headache seen for migraine in the emergency department/urgent care.

Diagnosis and treatment of headache: percentage of patients with decreased migraine headache shown by using a calendar or diary.

Diagnosis and treatment of headache: percentage of patients with migraine headache with treatment plans.

Diagnosis and treatment of headache: percentage of patients with migraine headache with a treatment plan who report adherence to their treatment plan.

Diagnosis and treatment of headache: percentage of patients with migraine headache with a prescription for opiates or barbiturates for the treatment of migraine.

Diagnosis and treatment of headache: percentage of patients with migraine headache prescribed appropriate acute treatment.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Beithon J, Gallenberg M, Johnson K, Kildahl P, Krenik J, Liebow M, Linbo L, Myers C, Peterson S, Schmidt J, Swanson J. Diagnosis and treatment of headache. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jan. 90 p. [140 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1998 Aug (revised 2013 Jan)

Guideline Developer(s)

Institute for Clinical Systems Improvement - Nonprofit Organization

Guideline Developer Comment

The Institute for Clinical Systems Improvement (ICSI) is comprised of 50+ medical group and hospital members representing 9,000 physicians in Minnesota and surrounding areas, and is sponsored by five nonprofit health plans. For a list of sponsors and participating organizations, see the [ICSI Web site](#) .

Source(s) of Funding

- The Institute for Clinical Systems Improvement (ICSI) provided the funding for this guideline. The annual dues of the member medical groups and sponsoring health plans fund ICSI's work. Individuals on the work group are not paid by ICSI, but are supported by their medical group for this work.
- ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups, and sponsoring health plans review and provide feedback but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

Guideline Committee

Committee on Evidence-Based Practice

Composition of Group That Authored the Guideline

Work Group Members: John Beithon, MD (*Work Group Leader*) (Lakeview Clinic) (Family Medicine); Jane Schmidt, NP (Affiliated Community Medical Center) (Nursing); Pamela Kildahl, RPh (HealthPartners Medical Group and Regions Hospital) (Pharmacy); Julie Krenik, MD (Hutchinson Medical Center) (Family Medicine); Mary Gallenberg, MD (Mayo Clinic) (Gynecology); Mark Liebow, MD (Mayo Clinic) (Internal Medicine); Linda Linbo, RN (Mayo Clinic) (Nursing); Jerry Swanson, MD (Mayo Clinic) (Neurology); Steven Peterson, PT (OSI Physical Therapy) (Physical Therapy); Kari Johnson, RN (Institute for Clinical Systems Improvement [ICSI]) (Facilitator); Cassie Myers (ICSI) (Facilitator)

Financial Disclosures/Conflicts of Interest

The Institute for Clinical Systems Improvement (ICSI) has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report *Clinical Practice Guidelines We Can Trust* (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These

members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI policy regarding Conflicts of Interest is available at the [ICSI Web site](#) .

Disclosure of Potential Conflicts of Interest

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National, Regional, Local Committee Affiliations: None

Guideline Related Activities: None

Research Grants: None

Financial/Non-Financial Conflicts of Interest: Spouse owns Pfizer stock from employer

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Guideline Related Activities: None

Research Grants: None

Financial/Non-Financial Conflicts of Interest: None

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Guideline Related Activities: None

Research Grants: None

Financial/Non-Financial Conflicts of Interest: None

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Guideline Related Activities: None

Research Grants: None

Financial/Non-Financial Conflicts of Interest: None

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Guideline Related Activities: None

Research Grants: None

Financial/Non-Financial Conflicts of Interest: None

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Guideline Related Activities: None

Research Grants: None

Financial/Non-Financial Conflicts of Interest: Receives compensation from UpToDate as a headache document editor

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of headache. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Jan. 84 p.

Guideline Availability

Available for purchase from the [Institute for Clinical Systems Improvement \(ICSI\) Web site](#) . Also available to ICSI members for free at the [ICSI Web site](#) and to Minnesota health care organizations free by request at the [ICSI Web site](#) .

Availability of Companion Documents

The following companion is provided to those who access the guideline (see the "Guideline Availability" field):

- Diagnosis and treatment of headache. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement; 2013 Jan. 2 p.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on February 5, 2003. The information was verified by the guideline developer on February 20, 2003. This summary was updated by ECRI on April 16, 2004 and January 25, 2005. This summary was updated on April 15, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated on February 10, 2006. This summary was updated by ECRI on August 29, 2006, following the U.S. Food and Drug Administration advisory on Triptans, SSRIs, and SNRIs. This summary was updated by ECRI Institute on May 17, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Gadolinium-based contrast agents. This summary was updated by ECRI Institute on June 20, 2007 following the U.S. Food and Drug Administration (FDA) advisory on gadolinium-based contrast agents. This NGC summary was updated by ECRI Institute on September 25, 2007. This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on April 1, 2009 following the FDA advisory on Reglan (metoclopramide). This summary was updated by ECRI Institute on September 16, 2009. This summary was updated by ECRI Institute on January 8, 2010 following the U.S. Food and Drug Administration advisory on Valproate sodium. This summary was updated by ECRI Institute on January 13, 2011 following the U.S. Food and Drug Administration (FDA) advisory on gadolinium-based contrast agents. This summary was updated by

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